PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

FOR FURTHER ACTION
See paragraph 2 below

Applicant's or agent's file reference
see form PCT/ISA/220

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/013744	30.11.2004	03.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D207/32, C07D401/04, A61K31/40, A61P29/00

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/013744

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7,8

because:

☒ the said international application, or the said claims Nos. 7,8 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-6,9,10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/013744

(III)
Claims 7,8 are directed to a method of treatment of the human/animal body and therefore no preliminary examination is required (Rule 67.1(iv) PCT).
Moreover, it is noted by the IPEA that for the assessment of Claims 7,8 on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, e.g., does not recognize the subject-matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

(V)
Having regard to the International Search Report document

D1: WO 98/25896 A (SEARLE & CO [US]; KHANNA ISH K [US]; WEIER RICHARD M [US]; YU YI [US]) 18 June 1998 (1998-06-18), in particular Ex.4-6 therein, with regard to present Rx/R1=opt.substituted alkyl, differ due to p-sulfonyl group compared with present o-ZRx substituent;

D2: EP-A-0 799 823 (SANKYO COMPANY LIMITED) 8 October 1997 (1997-10-08) differs due to present A-R1 group compared with R3 therein;

D3: WO 01/19814 A (MERCK FROSST CANADA & CO; LACOMBE, PATRICK; LABELLE, MARC; RUEL, REJEA) 22 March 2001 (2001-03-22) T.1 therein, discloses 2-thienyl analogue compounds;

D4: WO 03/084917 A (GLAXO GROUP LIMITED; GIBLIN, GERARD, MARTIN, PAUL; HALL, ADRIAN; HURST) 16 October 2003 (2003-10-16) discloses cyclopent-1-enyl analogue compounds.

The requirements of Art.33(2) PCT appear to be fulfilled.
Moreover, it is noted by the IPEA that P-document

D1: WO 03/101959 A (GLAXO GROUP LIMITED; GIBLIN, GERARD, MARTIN, PAUL; HALL, ADRIAN; HEALY) 11 December 2003 (2003-12-11), published after the claimed priority date and not relevant at this stage discloses numerous compounds falling under the scope of present formula (I) and having similar activity.

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International application No.
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The problem to be solved appears to be the provision of selective EP1 over EP3 PGE2-prostaglandine receptor antagonists of formula (I) according to Claim 1. Documents (D1)/(D2) disclose structurally similar antiinflammatory 1,2-diaryl derivatives. Doc.(D1), Ex.4-6 therein differs from the present compounds merely due to the position of the sulfonyl group on the 2-phenyl moiety. Doc.(D3)/(D4) teach the possibility of maintaining the antiinflammatory activity with variation of the central 5-membered ring, whereas the apparently essential 1,2-(hetero-)aryl groups are always present. (D3) discloses EP1 antagonistic activity without mentioning specifically the selectivity over EP3 receptors and (D4) discloses on p.166, l.1-3, similar selective EP1-antagonistic over EP3 affinitiy. In this respect reference is made to specific Ex.10-33 and 44-173 of (D4), which differ from the present pyrrole compounds due to the cyclopent-1-enyl group. It is considered that the skilled man, knowing from (D1)/(D3) that similarly substituted pyrrole and thienyl derivatives possess antiinflammatory activity, in combination with the PR1 selectivity over PR3 receptors known from (D4), would have expected that the exchange of the cyclopent-1-enyl moiety through the pyrrol-1-yl group would lead to further PR1 selective antagonists useful in treatment of inflammation and other prostaglandin mediated diseases.

Therefore, in the absence of an unexpected advantage over (D4) the requirements of Art.33(3) PCT do not appear to be fulfilled.

Moreover, reference is made in this respect to the broad and speculative definitions "optionally substituted; (bicyclic) heterocyclyl group; alk(en)yl" without further specification as disclosed on p.4, l.19-21 and p.9-10 of the description; the expression "pharmaceutically acceptable **derivatives**" includes all possible derivatives such as, e.g. prodrugs, and goes far beyond the anion definition for pharmaceutically acceptable salts given on p. 8 of the description.